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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/807,800	03/24/2004	Joseph Tucker	09741.0005-00000	4386

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EXAMINER	
OLSON, ERIC	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 08/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/807,800	TUCKER ET AL.	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *1,2,6,7 and 11-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-5 and 8-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *02/18/05, 04/14/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

This application is a continuation-in-part of 10/762796, which is a continuation-in-part of 10/222013, filed August 15, 2002, and also claims benefit of provisional applications 60/509156, filed October 7, 2003, 60/510669, filed October 10, 2003, and 60/510342, filed October 10, 2003.

Election/Restrictions

Applicant's provisional election of group III, drawn to a method of treating various conditions by administering a flavonoid or isoflavonoid compound as illustrated in claim 5, filed July 20, 2006, is acknowledged. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse. (MPEP § 818.03(a)) The requirement for restriction is therefore deemed proper and made FINAL.

Claims 1, 2, 6, 7, and 11-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on July 20, 2006.

Claims 3-5 and 8-10 are pending in this application and examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4-5 and 9-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Said claims are drawn to methods comprising administering a compound to a patient. The limitations of instant claims 4-5 and 9-10 define the patient population as "a patient," without indicating any characteristics of the patient, such as whether the patient is suffering from any clinical conditions or is in need of any treatments. Therefore instant claims 4-5 and 9-10 are indefinite.

Claims 3-5 and 8-10 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the structures of the compounds of claims 1 and 6. Note that both claims 1 and 6 are withdrawn from further consideration. Insertion of the recitation of the structures of claims 1 and 6 into claims 3-5 and 8-10, respectively, would be favorably considered.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3 and 8 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing serum cholesterol or blood pressure, and treating cardiovascular diseases linked to hypercholesterolemia and

hypertension, does not reasonably provide enablement for a method of treating any and all cardiovascular disorders, such as arrhythmias and congenital heart defects. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a method of treating cardiovascular, cholesterol, or lipid related disorders comprising administering to a patient a therapeutically effective amount of an active pharmaceutical compound.

The state of the prior art: Hypercholesterolemia is well known to be a major factor contributing to atherosclerosis and thus to various forms of cardiovascular disease. Hypertension is additionally a risk factor for heart attack and stroke. Treating hypercholesterolemia and hypertension is therefore a recognized therapy for patients at risk of cardiovascular disorders due to cholesterol or blood pressure.

Flavonoids and isoflavonoids are known in the prior art to reduce LDL levels and increase HDL levels, thus providing an effective treatment for hypercholesterolemia. Nitric oxide, generally delivered as a NO-donor drug such as nitroglycerin or NO-aspirin is also known to exert hypocholesterolemic effects, and additionally to lower blood pressure.

Cardiac arrhythmias are episodes of abnormal heart rate that due to abnormalities in the electrical system cells which control the heart rate. They are typically treated with ion channel blockers or implanted pacemakers or defibrillators. (The Merck Manual, Seventeenth Edition, included with PTO-892, herein referred to as Merck, pp. 1714-1720) Arrhythmias are not treated by lowering cholesterol or blood pressure. Thus the prior art does not provide any basis for using flavonoids, isoflavonoids, or NO-donors as therapeutics for the treatment of arrhythmias.

Congenital heart defects are inherent abnormalities in the heart which are present at birth and which are often genetically determined. They are not related to or caused by elevated cholesterol, lipids, or blood pressure. Some congenital heart defects may be repaired with surgery, but drug treatment with cholesterol-lowering drugs is not a recognized therapy for these conditions.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: According to Merck (p. 1713, right column, last paragraph – p. 1714, left column, first paragraph) "there is no universally effective drug; [for treating arrhythmias] all have important safety limitations and can

aggravate or promote arrhythmias. Drug selection is difficult and often involves trial and error." Therefore drug therapy for arrhythmias is unpredictable.

Congenital heart defects include a diverse range of conditions including but not limited to atrial septal defects, complete atrioventricular defects, partial atrioventricular canal defects, ventricular septal defects, underdeveloped left ventricle syndrome, teratology of fallout, transposition of the great arteries, and other syndromes involving congenital defects of the heart. (Merck, pp. 2198-2210) Thus the treatment of congenital heart defects is expected to be highly unpredictable.

The Breadth of the claims: The instant claims are drawn to methods of treating any cardiovascular disorders, and any cholesterol or lipid related disorder. This breadth includes cardiovascular disorders not related to lipids or hyperlipidemia, such as arrhythmias, congenital heart defects, and congestive heart failure.

The amount of direction or guidance presented: Applicant's specification discloses various methods for testing the cholesterol-lowering activity of the disclosed compounds. Applicant's specification provides no guidance for determining a compound's anti-arrhythmia activity, nor evidence suggesting that the disclosed NO-donating compounds would be useful as anti-arrhythmia drugs or treatments for congenital heart defects.

The presence or absence of working examples: Applicant's specification provides no working examples of any methods for treating arrhythmias or congenital heart defects by administering the disclosed compounds.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as drug therapy of arrhythmias. See MPEP 2164.

The quantity of experimentation necessary: In order to practice the claimed invention for the treatment of all cardiovascular disorders including arrhythmias and congenital heart defects, one skilled in the art would undertake to test the claimed compounds for various models of arrhythmias and congenital heart defects. Because both of these classes of conditions are complex and unpredictable, multiple *in vivo* models will be needed for these diseases. *In vivo* animal models involve, in addition to the actual experimentation, an additional burden associated with the care and feeding of the animals, compliance with ethical and regulatory requirements, and disposal of dead animals after the experiment. Because there is no evidence in the prior art or in Applicant's disclosure suggesting that the claimed compounds are useful for treating arrhythmias or congenital heart defects, one skilled in the art would have no expectation of success in developing these methods. For these reasons, one skilled in the art would face an undue burden of unpredictable experimentation in order to practice the claimed invention.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the state of the prior art and the lack of guidance or working examples in Applicant's disclosure, Applicants fail to provide information sufficient to practice the claimed invention for the treatment of cardiovascular disorders not caused by hyperlipidemia or hypertension.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bok et al. (US patent 6133241, reference cited in PTO-1449) in view of Chrysselis et al. (Reference cited in PTO-1449)

Bok et al. discloses a method of increasing the plasma HDL level in a mammal comprising administering a flavonoid compound. (Column 2, line 34 – column 3, line 10) Preferred embodiments of the invention of Bok et al. involve specific flavonoids disclosed in column 3, lines 22-42, table II. Examples 2-4 disclose specific working examples in which hesperidin and naringin were administered to rats or humans, resulting in a decrease in total cholesterol and an increase in HDL cholesterol. (column 6, line 38 – column 8, line 67) Bok et al. also discloses that bioflavonoids are useful as antioxidants and antihypertensives. (column 2, lines 20-29) Bok et al. does not disclose

a method comprising administering a flavonoid NO-donor derivative to a patient as disclosed by instant claims 3-5. This procedure is reasonably considered to be a method of treating cardiovascular, cholesterol, or lipid related disorders and reducing serum cholesterol by administering a flavonoid compound. Bok et al. does not disclose a similar method comprising administering a nitrated flavonoid compound as disclosed by instant claims 3-5.

Chrysselis et al. discloses a number of nitric oxide donor compounds comprising an organic small molecule with hypolipidemic and antioxidant activity and an attached nitrate moiety. (p. 5406, left column, second paragraph) These compounds simultaneously every an activity as organic small molecule drugs and additionally release nitric oxide which provides additional anti-atherogenic activity. Nitric oxide donating ability was found to be inversely correlated with lipophilicity. (p. 5407, left column, last paragraph – right column, first paragraph) The compounds were administered to hyperlipidemic rats, and caused a decrease in total cholesterol, triglycerides, and LDL. (p. 5407, right column, second paragraph, p. 5407, left column, table 1)

It would have been obvious to one of ordinary skill in the art at the time of the invention to prepare a nitrated flavonoid compound by substituting one or more of the hydroxyl groups of any of the flavonoids disclosed by Bok et al. with a nitrate group, and to administer the resulting compound to a hypercholesterolemic or hyperlipidemic patient (i.e. one who is in need treatment) as disclosed in instant claims 3-5. One of ordinary skill in the art would have been motivated to modify the invention in this way

because the compounds of Bok et al. have the same biological activity (e.g. antioxidant and hypocholesterolemic) as the compounds used as NO-donor scaffolds by Chrysselis et al., and possess additional activities (HDL-increasing and blood-pressure-lowering) which would be useful in treating hyperlipidemic patients at risk for heart disease, and additionally because, being less lipophilic than the compounds of Chrysselis et al., these compounds would be expected to be better NO-donors. One of ordinary skill in the art would reasonably have expected success in modifying the invention in this way because Chrysselis et al. already demonstrate that modifying a cholesterol-lowering drug with a nitrate group can cause it to serve as a NO-donor and increase its hypocholesterolemic activity.

Therefore the invention taken as a whole is *prima facie* obvious.

Claims 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodman-Gruen et al. (Reference included with PTO-892) in view of Chrysselis et al. (Reference cited in PTO-1449) Goodman-Gruen et al. discloses that consumption of the isoflavonoid compounds genistein or daidzein correlates with increased HDL levels in human subjects. (p. 1203, right column, fifth paragraph, p. 1205, left column, first paragraph) Thus these compounds are useful as HDL-increasing agents and may be used in a method of treating hyperlipidemia or cardiovascular disease related to cholesterol by administering them to a patient suffering from these conditions. Goodman-Greun et al. does not disclose a method of treating hyperlipidemia or

cardiovascular disease related to cholesterol by administering to a patient suffering therefrom a nitrated derivative of genistein or daidzein.

The disclosure of Chrysselis et al. is discussed above in a previous rejection.

It would have been obvious to one of ordinary skill in the art at the time of the invention to prepare a nitrated isoflavonoid compound by substituting one or more of the hydroxyl groups of genistein of daidzein with a nitrate group, and to administer the resulting compound to a hypercholesterolemic or hyperlipidemic patient (i.e. one who is in need treatment) as disclosed in instant claims 8-10. One of ordinary skill in the art would have been motivated to modify the invention in this way because these compounds are disclosed by Goodman-Gruen et al. to exert a positive effect on HDL levels, and thus to be useful for treating the same patient population as the compounds used as NO-donor scaffolds by Chrysselis et al., namely hyperlipidemic patients and those at risk for lipid-associated cardiovascular disease, and additionally because, being less lipophilic than the compounds of Chrysselis et al., these compounds would be expected to be better NO-donors. One of ordinary skill in the art would reasonably have expected success in modifying the invention in this way because Chrysselis et al. already demonstrate that modifying a cholesterol-lowering drug with a nitrate group can cause it to serve as a NO-donor and increase its usefulness in treating hypercholesterolemia.

Therefore the invention taken as a whole is *prima facie* obvious.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. These documents include: Lamon-Fava, Theriault et al., Wangen et al., Pace-Asciak et al., Li et al., Ahn et al., Law et al., and US patents 5763414, 5877208, and 6165984. (References included with either PTO-1449 or PTO-892) These references disclose additional flavonoid and isoflavonoid compounds possessing one or more of the following activities:

(i) Increasing HDL in a human subject.

(ii) Decreasing LDL in a human subject.

(iii) Promoting ApoA1 expression in mammalian cells.

Additionally, Law et al. discloses that flavonoid antioxidants are capable of neutralizing the unwanted free-radical activity of nitric oxide and its oxidation product preoxynitrite and thus protecting the aortic endothelial cells from free radical damage which would otherwise be caused by elevated nitric oxide, either endogenous or released by a nitric oxide donor.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 3-5 and 8-10 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 3-5 and 8-10 of copending Application No. 10/762796. (Reference cited in PTO-892, herein referred to as '796) Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 6-8 and 10-12 of '796 anticipate instant claims 3-5 and 8-10. Claims 6 and 10 of '796 are drawn to a method of treating cardiovascular or lipid related disorders in a patient comprising administering to a patient in need of treatment a therapeutically effective amount of, respectively, a flavonoid or isoflavonoid compound according to claim 5 or 9, respectively. These flavonoid and isoflavonoid compounds are drawn to compounds of a range of structures which falls completely with the scope of compounds of the claimed invention of instant claims 3-5 and 8-10. Claims 7-8 and 11-12 of '796 are drawn to similar methods comprising administering to a patient a therapeutically effective amount of the claimed compounds. These claims are of closely overlapping scope with instant claims 4-5 and 9-10. Claims 6-8 and 10-12 of '796 thus anticipate instant claims 3-5 and 8-10.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Summary

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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